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Movement disorders and nonmotor neuropsychological symptoms in children and adults with classical galactosemia

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Abstract

Although movement disorders (MDs) are known complications, the exact frequency and severity remains uncertain in patients with classical galactosemia, especially in children. We determined the frequency, classification and severity of MDs in a cohort of pediatric and adult galactosemia patients, and assessed the association with nonmotor neuropsychological symptoms and daily functioning. Patients from seven centers in the United Kingdom and the Netherlands with a confirmed galactosemia diagnosis were invited to participate. A videotaped neurological examination was performed and an expert panel scored the presence, classification and severity of MDs. Disease characteristics, nonmotor neuropsychological symptoms, and daily functioning were evaluated with structured interviews and validated questionnaires (Achenbach, Vineland, Health Assessment Questionnaire, SIP68). We recruited 37 patients; 19 adults (mean age 32.6 years) and 18 children (mean age 10.7 years). Subjective self-reports revealed motor symptoms in 19/37 (51.4%), similar to the objective (video) assessment, with MDs in 18/37 patients (48.6%). The objective severity scores were moderate to severe in one third (6/37). Dystonia was the overall major feature, with additional tremor in adults, and myoclonus in children. Behavioral or psychiatric problems were present in 47.2%, mostly

internalizing problems, and associated with MDs. Daily functioning was significantly impaired in the majority of patients. Only one patient received symptomatic treatment for MDs. We show that MDs and nonmotor neuropsychological symptoms are frequent in both children and adults with classical galactosemia.

KEYWORDS

galactosemia, dystonia, tremor, daily functioning, nonmotor symptoms

1 | INTRODUCTION

Classical galactosemia (OMIM: 230400) is an inborn error of galactose metabolism, caused by a severe deficiency of the galactose-1-phosphate uridyltransferase (EC 2.7.7.12) enzyme. After ingestion of galactose in infancy, the accumulation of galactose-1-phosphate and its metabolites results in multi-organ failure with predominant involvement of the liver. In particular newborns are susceptible for severe *Escherichia coli* sepsis. The mainstay of treatment is a galactose-restricted and lactose free diet, which is lifesaving when started early.

Despite this treatment many patients develop long-term complications.[1,2] The most frequent and severe long-term complications are impaired cognition, speech and language deficits, and in women premature ovarian failure.[3] Next to these well-known complications, galactosemia is increasingly being recognized as a neurometabolic disorder with significant motor involvement.[3–5] In particular tremor and ataxia have been reported.[1,4,6] However, in most papers, data were collected retrospectively or without formal neurological examination and quantification of the severity of symptoms.[2,6,7] Two more detailed and recent papers evaluated movement disorders (MDs) in adult galactosemia patients by direct neurological examination. Waisbren et al studied 33 adult patients and found tremor being most frequent (46%), followed by ataxia (15%), and dystonia (6%).[3] Rubio-Agusti et al investigated MDs in 47 adult patients.[8] They reported motor dysfunction in 66%. Tremor was seen in 49%, ataxia in 13%, and a remarkably higher frequency of dystonia (49%) than earlier reported. Detailed information about MDs in particular in children with galactosemia is currently scarce and possible differences between children and adults are largely unknown.

In galactosemia a high prevalence of depression and anxiety has been reported. In patients with (primary) MDs there is also an increasing awareness of associated nonmotor neuropsychological symptoms.[9–11] Whether these symptoms are secondary to the burden of a MD or part of the phenotype is still unsolved. It is interesting to evaluate whether the motor and nonmotor symptoms are associated in galactosemia patients.[3,8]

The aim of this study is to systematically determine the frequency, classification and severity of MDs in a cohort of adult and pediatric galactosemia patients, and to assess the association with clinical characteristics, such as treatment variables. We will also evaluate nonmotor neuropsychological symptoms and daily functioning and analyze whether these are associated with the presence of MDs.

2 | METHODS

Patients were recruited from the metabolic departments of five nationally endorsed centers of expertise in the Netherlands and two in the United Kingdom. All patients, both children (<18 years) and adults (≥18 years), with a genetically or enzymatically confirmed diagnosis of classical galactosemia were invited to participate. Written informed consent has been obtained from all participants or their official caregivers. This study was approved by the medical ethics committees of the participating centers, and carried out in accordance with the Declaration of Helsinki.

Self-perceived motor symptoms were evaluated with a structured interview. Demographic and disease characteristics were obtained by interviewing and/or from patient files. To determine the presence, classification and severity of MDs, a standardized videotaped neurological examination was performed (A.K.). This protocol included walking, posturing tasks, kinetic tasks, and functional tasks such as writing. The motor phenotype was scored during consensus meetings using the videos. The expert panel (M.T., T.K., R.Z., H.E., A.K.) was briefly informed about the clinical history and self-reported symptoms. The dominant and any associated MD types were identified. Severity of each MD was determined with the Clinical Global Impression severity scale (CGI, a 7-point Likert scale, higher scores indicate a more severe MD).[12]

Adaptive and daily functioning and psychiatric and behavioral problems were assessed with age-specific validated Dutch and English questionnaires. In children we assessed adaptive functioning with the Vineland Adaptive Behavior Scale,[13] and scores were transformed in a

developmental age equivalent. Subsequently, the percentage of age-appropriate functioning (developmental age/biological age × 100%) was determined. Daily functioning in adults was evaluated with the Health Assessment Questionnaire (HAQ),[14] providing a Functional Disability Index (FDI, range 0-3, higher scores indicating more disability), and with the Sickness Impact Profile (SIP68, range 0-68, higher score indicating more disability).[15] The presence of various domains of psychiatric and behavioral problems were identified with age-appropriate versions of the Achenbach questionnaires, using both a self-report and proxy version (Child Behavior Checklist and Youth Self Report, Adult Behavior Checklist, and Adult Self report).[16–18]

Statistical analyses were carried out using SPSS version 23. Univariate logistic regression was used to calculate odds ratios for MD presence according to clinical or demographic characteristics. To assess differences in MD frequencies, the Fisher's exact test was used. Differences in continuous variables between patients with and without MDs were analyzed with the Independent samples *t* test or Mann-Whitney *U* test, depending on normality of the data.

This study was approved by the medical ethics committees of the participating centers. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Written informed consent has been obtained from all participants included in the study or their official caregivers.

This article does not contain any studies with human or animal subjects performed by the any of the authors.

3 | RESULTS

Thirty seven patients were recruited (15 males, 22 females), from 29 different families (eight pairs of siblings). The participation rate was 70% (37/53). The cohort contained 19 adult patients (mean age 32.6 years) and 18 children (mean age 11.0 years). Four of the adult patients reported here, were also included in the study by Rubio-Agusti et al[8] Table 1 presents the demographic and disease characteristics.

TABLE 1 Demographic and disease characteristics (n = 37)

Gender	
Male	40.50%
Female	59.50%
Age group	
Children (<18y)	48.60%
Adults (≥18y)	52.40%
Age (years) mean (SD)	
Adults	32.6y (8.4)
Children (<18y)	11.0y (5.4)
Country of residence	
Netherlands	81.10%
United Kingdom	18.90%
Time of diagnosis	
Median age in days (IQR)	8 (15)
Early (within 2 weeks of age)	73%
Late (after 2 weeks of age)	27%
Reason for diagnosis	
Clinical symptoms	75.70%
New-born screening[a]	13.50%
Sibling screen	10.80%
Reported dietary adherence	
Strict adherence	83.80%
Minor variability in adherence	13.50%
Longer nonadherent periods	2.70%
Educational level adults	
Special needs or primary school	4/19 (21.1%)
Lower vocational education	4/19 (21.1%)
Secondary education	10/19 (51.6%)
Higher education	1/19 (5.3%)
Motor milestones	
In time	67.60%
Delayed	32.40%

Abbreviations: IQR, interquartile range.

Values represent frequencies in percentages. Age is represented as mean (SD), and age at diagnosis as median (IQR).

[a]New born screening for galactosemia was introduced in The Netherlands in 2007.

3.1 | Self-perceived motor symptoms

The structured self-report revealed subjective motor symptoms in 19/37 patients (51.4%, 5 children, 14 adults). Twelve of them reported problems with fine motor tasks (writing and closing buttons) as well as gross motor skills (running or balance), four had difficulties only with fine motor tasks, and three patients only gross motor problems. The rate of self-reported motor problems was similar to the frequency of MDs observed with the video assessment, but these frequencies do not comprise exactly the same patients. Three patients who were found to have MDs based on the video examination did not report motor problems themselves. On the other hand, four patients reported motor symptoms themselves (one intermittent trembling of the hands, three problems with gross motor skills) while no MDs were detected during the video examination.

In 7/19 (36.8%), all adults, these symptoms were reported progressive. The majority of patients (78.9%) indicated that

their motor symptoms had already started before the age of 10 years, in two it started as between 10 and 20 years, in one patient between 20 and 40 years, and in one after the age of 40.

3.2 | Movement disorder assessment

Based on videotape evaluation by the expert panel, MDs were present in 18/37 patients (48.6%). In the pediatric group the total frequency of MDs was 38.9% and in adults 57.9% (Fisher's exact test $P = 0.330$). In the majority (10/18) more than one MD was present simultaneously. MDs were predominantly scored as mild (maximal CGI 3), but in one third (6/18) MDs were at least moderate (CGI 4-7). Table 2 presents the type, severity, and distribution of MDs.

Dystonia was most frequently observed (3 children, 9 adults). In all but one dystonia was the predominant MD type. The dystonic symptoms were mild in the majority of cases, but in three patients classified as moderate (CGI 4), and in one as severe generalized dystonia (CGI 6). The upper limbs were most often affected (n = 9) and five patients had a torticollis. When only the upper limbs were affected, dystonia was often action-specific, while in case of a generalized or segmental distribution including the neck or trunk a more persistent pattern was seen.

Tremor was the second most common MD, present in 1 child and 5 adults. The severity of tremor ranged from minimal (CGI 2) to marked (CGI 5). The tremor was limited to the upper limbs in most patients, in three the head was also tremulous. In one patient a jaw tremor was observed. Tremor was frequently seen in combination with dystonic features (4/6). In three patients the tremor could be characterized as a fast bilateral combined intention and action tremor, in one as only a mild intentional tremor. In two other patients the tremor was more distal, postural, fast, and with a

TABLE 2 Details of the observed MDs by video examination

Patient (sex, age)	Overall CGI	Predominant MD		Associated MD		Other neurological signs
		Type	CGI	Type	CGI	
M, 2y	2	Stereotypies	2		1	Hemi spasticity R
M, 9y	4	Dystonia: UL (R&L), N, persistent	4	Chorea: G	3	
M, 11y	3	Dystonia: UL (L > R), action specific	3	Tics, stereotypies	2	Mirror movements
M, 13y	3	Ataxia: UL (R&L)	3	Myoclonus: UL (R&L)	3	
M, 13y	3	Dystonia: T, UL (R&L), action specific	3	Myoclonus: T & UL (R&L)	2	Mirror movements
F, 16y	4	Tremor: UL (L > R): action & intention, fast, small amplitude	4	Myoclonus: UL (R&L)	2	
M, 17y	2	Myoclonus: G	2		1	Mirror movements
F, 19y	5	Tremor: UL (R&L): action & intention, fast, large amplitude	5	Dystonia: N & UL (R&L), action-specific	2	
F, 23y	2	Dystonia: N, persistent	2		1	
F, 24y	2	Tremor: UL (R&L): postural, fast, small amplitude	2	Ataxia: UL (R&L)	2	
F, 25y	6	Dystonia: G, persistent	6	Ataxia:: UL, LL, gait	3	
M, 30y	2	Dystonia: UL (L), action specific	2	Tics, stereotypies	2	
F, 31y	2	Dystonia: UL (R), persistent	2		1	
M, 35y	3	Dystonia: N&T, persistent	3	Tremor: UL (R): intention, fast, small amplitude	2	
F, 40y	4	Dystonia: UL (R > L), N, persistent	4	Tremor: UL (R&L), H: action & intention, slow, large amplitude	4	
F, 43y	3	Dystonia: UL (L > R), action specific	3		1	
F, 44y	2	Dystonia: UL (L), action specific	2		1	
F, 50y	4	Dystonia: UL (R > L), N, persistent	4	Tremor: UL (R > L), H, J: rest & intention, slow, large amplitude Ataxia: UL (R&L)	3	

Abbreviations: MD, movement disorder; CGI, Clinical Global Impression severity scale, values represent the following: 1, no MD; 2, minimal signs of a MD; 3, mild MD; 4, moderate MD; 5, marked MD; 6, severe MD; 7, among most extremely affected patients.
UL, upper limb(s); LL, lower limb(s); N, neck; H, head; T, trunk; G, generalized; J, jaw; R, right; L, left.

small amplitude. In one patient a slower rest tremor was seen, with larger amplitude.

Myoclonus was found in four children. Myoclonus was mild and in only one patient generalized and the dominant MD type. In the others it was associated with either dystonia, tremor, or ataxia and affected the upper limbs, mostly distal. Myoclonus was in all cases provoked by action and not stimulus sensitive.

Other MDs and motor symptoms included ataxia, tics, stereotypies, and spasticity. In four patients, one child and three adults, ataxia was seen and in three of them ataxia was not the dominant feature but associated with dystonia or tremor. Ataxic signs consisted of upper limb dysmetria and dysdiadochokinesis in three patients and in one there was a more extended picture with involvement of lower limbs and gait ataxia as well. Three patients had tics or stereotypies, all in the context of psychomotor retardation or autism. One boy with a history of intracranial bleeding in infancy had spasticity. Further, speech problems were frequent (59.5%), consisting of word-finding difficulties or stuttering rather than dysarthria. One patient had a spasmodic dysphonia.

In our cohort there was only one patient, suffering from generalized dystonia and ataxia, who received specific MD treatment (trihexyphenidyl, botulinum toxin injections, and a lycra suit). Ten patients had supportive therapy such as physiotherapy or occupational therapy at some point in their lives.

3.3 | Nonmotor findings

Eight patients (21.6%) had at least one psychiatric diagnosis in their past and were all treated for this. Four patients were diagnosed with an autism spectrum disorder, three with attention deficit hyperactivity disorder (ADHD), two with a depression, one had generalized anxiety, and one had had a psychotic episode.

The Achenbach questionnaires revealed behavioral problems on at least one of the evaluated domains in 47.2%. Internalizing problems were most frequent; 38.9% had a deviant score (either borderline range (n = 3) or clinical range (n = 11)) when assessed by proxy-report (available in 36 patients). When assessed with self-report (available in 26 patients), internalizing problems were found in 26.9%. The most contributing subdomain was withdrawn/depressed, abnormal in 33.3% respectively 30.8% (proxy and self-report), followed by anxious/depressed, abnormal in 16.7% and 19.2%. See supplementary Table 1, Supporting Information for T-scores on the different domains.

3.4 | Daily functioning

The mean level of adaptive functioning in the children in our cohort was only 68.8% of their age-appropriate functioning. All three subdomains (communication, daily activities, and social skills) were affected, with the daily activities showing the largest delay. (Data shown in Supplementary Table 2).

The median FDI of adult patients was 0.06 (interquartile range [IQR] 0.41); slightly higher than the median score of 0.00 in corresponding age groups in the general population.[14] A few patients had considerably more functional impairment; the highest score was 2.50. Overall, almost half of the adult patients (47.4%) had some form of disability (FDI > 0), a higher percentage than in corresponding age groups in the general population (8.5% to 25.0% in ages 30 to 50).[14] The median score on the SIP68, also assessing impact on daily life, was 4.5 (IQR 9). No normative values are available, but the level of disability in this cohort was lower than reported for patients with acute traumatic brain injury (mean SIP68 score 15.6 ± 11.5)[19] or acute stroke (mean score 41.2 ± 11.7)[20] However, again we saw some outliers in our cohort with considerable disability (highest score 30). Furthermore, 6/19 adult patients (31.6%) had to use an aid or device for their daily activities, such as a wheelchair, bath seat, or a tray to carry things.

3.5 | Factors associated with the presence of MDs

We performed a univariate logistic regression analysis to identify whether clinical factors, such as age at diagnosis or dietary adherence, are associated with the presence of MDs (Table 3). MDs were not significantly more frequent among patients diagnosed late (later than 2 weeks of age [cut off based on Ref. 21]) than those diagnosed within 2 weeks of age We also found no differences in MD frequency between groups with higher or lower dietary adherence. However, a delay in motor milestones was strongly associated with the presence of MDs (odds ratio 28.29, $P = 0.003$).

MDs were found more frequently in children receiving special education than in those attending regular education (80.0% vs 22.2%), and more frequently in adults who were unemployed than in those who had a paid job (88.5% vs 40.0%), although these differences did not reach statistical significance ($P = 0.055$ and $P = 0.060$).

We found a significant association between MDs and internalizing behavioral problems; MDs were present in 71.4% vs 31.8% of the patients respectively with (n = 14) and without (n = 22) internalizing problems (Fisher's exact $P = 0.023$). This association with MD presence was also found for the subdomain anxious/depressed, MDs were observed in 100% (n = 6) vs 36.7% (n = 30) in patients respectively with and without these psychiatric problems

TABLE 3 Associations of clinical variables with the presence of MDs

	Frequency of MDs	OR (95% CI)	*P*-value*
Male vs female	53.3% vs 45.5%	1.37 (0.37-5.12)	0.638
Adults vs children	57.9% vs 38.9%	2.16 (0.58-8.04)	0.251
Late (>2wks) vs early diagnosis (and treatment)	60.0% vs 44.4%	1.98 (0.43-8.20)	0.404
Some dietary inaccuracies vs strict dietary compliance	50.0% vs 48.4%	1.07 (0.19-6.13)	0.942
Delayed motor milestones vs normal motor development	91.7% vs 28.0%	12.25 (1.08-138.99)	***<0.001***
Speech problems vs no speech problems	59.1% vs 33.3%	2.89 (0.74-11.36)	0.129
Fertility problems vs no fertility problems (women)	50.0% vs 66.7%	0.50 (0.04-6.55)	0.597
Special education vs normal education (school children)	80.0% vs 22.2%	14.00 (0.94-207.60)	0.055
Currently unemployed vs employed (adults)	87.5% vs 40.0%	10.50 (0.91-121.39)	0.060

Abbreviations: CI, confidence interval; MD, movement disorders; OR, odds ratio.
**P*-value based on univariate logistic regression analysis.

(Fisher's exact $P = 0.006$). The age- and sex-adjusted T-scores for internalizing problems, the anxious/depressed subdomain, and total behavioral problems (proxy reports) were significantly higher in patients with MDs than in those without (Supplementary Table 1).

When assessing adaptive functioning in children, the score on the communication domain differed most and significantly between patients with and without MDs (68.5% vs 95.5%, $P = 0.009$). The scores on the other two subdomains and the total score were also lower in children with MDs, not reaching statistical significance. (Supplementary Table 2) The adult patients with MDs had a somewhat higher FDI than those without (median scores 0.13 vs 0.00), but this difference was not significant (Mann-Whitney *U* $P = 0{,}304$). The same is true for the SIP68 score; patients with MDs had a slightly higher median SIP68 score (7.5 vs 3.5, Mann-Whitney *U* $P = 0.109$).

4 | DISCUSSION

This is the first comprehensive study reporting a systematic and detailed evaluation of MDs together with nonmotor neuropsychological symptoms and the impact on daily functioning in both children and adults with classical galactosemia.

MDs were found in almost half of the patients. This frequency is in line with the earlier reports in adults (45 and 66%) (3.8). The MD prevalence could be an overestimation since there might have been a selection bias; patients suffering from MDs may be more inclined to participate in research addressing this topic. The participation rate of our study was relatively high (70%), thereby reducing this possible selection bias. In respect of the prevalence and severity of MDs we found, it is remarkable that only one patient in our cohort received specific MD treatment.

Dystonia and tremor were the major MD types in adults, which is in accordance with the dominant MD types reported by Rubio-Agusti et al.[8] Similar to what is known for other inborn errors of metabolism (IEM) with MDs,[22] the majority of patients had a combined MD phenotype with different MD types being present simultaneously.

One of the strengths of the present study is the inclusion of both children and adults, allowing us to demonstrate remarkable differences in MD types. Dystonia and myoclonus dominated the phenotype in children, while in adults no myoclonus was detected. This suggests evolution of MDs over time. Possibly, MD appearance in childhood is influenced by development, immaturity, and ongoing myelination of the central nervous system (CNS), while later in life the MDs evolve to a more tremulous appearance. It would be interesting to see whether a similar difference between children and adults is seen in other IEM with MDs.

Next to the video assessment, we interviewed patients about self-perceived motor symptoms. We found less discrepancy between the self-report and the expert evaluation than in earlier reports.[8] The majority of patients in our study indicate that their motor symptoms started in childhood, but later beginning was also described. Almost 40% of the patients with MDs report their motor symptoms to be progressive, remarkably only reported by adults. A limitation of this study is that data on the course of symptoms were collected retrospectively and were self-reported. Longitudinal studies are required to further clarify when MDs occur and whether these are indeed progressing or evolving in time.

It is not well understood why some galactosemia patients develop a severe neurological phenotype and others do not. In many IEM an early diagnosis and treatment is very important for the clinical (neurological) outcome. However, in our cohort this association was not found. This is in accordance with earlier studies in galactosemia.[1,8,23] It seems that, although obviously of undisputed importance, early

initiation of treatment does not always prevent MDs. Moreover, in our study there were two pairs of siblings of whom the youngest were diagnosed and treated from day one and had much more severe MDs than the late diagnosed older sibs. This was also described within a family reported by Hughes et al.[6] Strict dietary adherence also cannot prevent MDs. Dietary adherence was very high in our patient group, but patients who had noncompliant periods did not have more MDs. Too strict dietary regimens with over-restriction of galactose might even have negative effects. This hypothesis has also been suggested by Knerr et al,[24] and similar phenomena were also described in other IEM, like urea cycle defects.[25] These findings might be explained by accumulation of toxic metabolites on one hand, and lack of relevant (intermediary) metabolites on the other hand. Based on current knowledge, we assume that both ends of the spectrum, late/no dietary treatment as well as a very restricted diet, would not lead to optimal (motor) functioning.

In our study we found an association between a history of delayed motor milestones and the occurrence of MDs. This is an important finding, as it can serve as a "red flag." We advise extra alertness for the occurrence of MDs in children with galactosemia who have a delayed motor development. Based on our results, the occurrence of MDs seems to be based on an individual susceptibility rather than on treatment characteristics. Our findings might indicate that patients with MDs have a more severe phenotype in general, as we also observed a trend that MDs were more frequent in patients with speech problems, children who attend special education and in adults who are unemployed. Although we did not demonstrate statistically significant differences for these parameters, the found differences are of reasonable magnitude and should be interpreted in the light of the relatively small sample size. Despite lacking statistical power, the differences might very well be relevant.

Next to MDs, a high percentage of patients in our study had behavioral or psychiatric problems (47.2%), associated with the presence of MDs. Internalizing symptoms such as depression and anxiety, were most frequent (38.9%). This is in accordance with earlier reports on psychiatric comorbidity in galactosemia with high rates of anxiety and depression.[3,8] It is interesting to speculate whether these symptoms are a secondary phenomenon to physical or cognitive disability or if they are part of the disease itself. In recent years it has become clear that nonmotor neuropsychological symptoms form an integral part of several primary MDs such as idiopathic cervical dystonia or dopa-responsive dystonia.[9,10] The fact that in our study psychiatric and behavioral symptoms were associated with MDs and were often co-occurring outlines the possibility that in galactosemia there might also be a common pathophysiological pathway affecting both motor and nonmotor circuits. Unfortunately, in our study we had no electrophysiological registrations or magnetic resonance imaging (MRI) or neurotransmitter imaging data available. To further elucidate the pathophysiology of MDs and neuropsychological symptoms in patients with galactosemia, it is important to incorporate the results of these diagnostic tests and clinical data in future studies.

Impairment in daily and adaptive functioning was common in our cohort. Patients with MDs had lower levels of adaptive functioning; especially the communication domain appeared associated with MDs. To improve the level of functioning of our patients, MDs are important to take into account and should be considered for symptomatic treatment and supportive therapies.

In conclusion, hyperkinetic MDs are frequent in both children and adults with galactosemia. We found remarkable differences in the clinical presentation between children and adults. The occurrence of MDs seems to be based on an individual susceptibility rather than treatment characteristics. Longitudinal studies are needed to further elucidate the evolvement of MDs. We demonstrated an association between MDs and nonmotor neuropsychological symptoms and a lower level of daily functioning. Based on the results of our study, we recommend an increased awareness of both MDs and nonmotor neuropsychological symptoms in patients with galactosemia. When applicable, treatment of MDs should be considered. Patients would benefit from regular and detailed neurological and neuropsychological assessments; the inclusion of these assessments in galactosemia guidelines is supported by this research.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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